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1806

06/01/94

☒ This application has been examined

☒ Responsive to communication filed on 11/3/93
8/23/93

☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|--|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input checked="" type="checkbox"/> Notice re Patent Drawing, PTO-946. |
| 3. <input checked="" type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, Form PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> |

Part II SUMMARY OF ACTION

1. ☒ Claims 1-33 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-33 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-946).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received
☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

15. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title should be addressed to the specificity which relies on a common epitope between E-selectin and L-selectin.

16. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948. Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views).

17. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

18. Claims 3-5, 10-18, 21-23 and 26-33 are rejected under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks utility. The specification fails to establish the utility of the claimed E-/L-selectin specific antibodies as therapeutic agents for human disease. Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3) (Tibtech, 1993). Humanized antibodies present serious problems with immunogenicity, since the idioype of such antibodies will contain unique amino acid sequences. Concerning selectin-mediated therapy, Harlan states that "whether you go humanized antibody, peptide soluble receptor, or saccharide, it's still a long way to a product" (1449, #4; Edgington, Biotechnology, 1992, page 386, column 3, paragraph 4). Furthermore, the therapeutic indices of drugs or biopharmaceuticals are often species- and model-dependent. Applicant has not provided any evidence a priori that establishes

the efficacy of the claimed invention for the treatment of human disease. Therefore it does not appear that the asserted utility of the claimed methods or compositions for treating humans would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. See MPEP 608.01 (p).

Although claims 21-23 are claimed as compounds, their intended use or limitation is therapeutic. If applicant is not relying on these limitations, then the claims should be deleted as they would not further limit the independent claimed compound. If applicant is attempting to claim pharmaceutical compositions, then the claims should be recited as such.

19. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present the best mode contemplated by the applicant for carrying out the invention.

A) Applicant has not disclosed how to use E-/L-selectin-specific antibodies therapeutically in humans. There is insufficient written description of the invention with respect to the in vivo operability of E-/L-selectin-specific antibodies to use applicant's invention for the reasons discussed in detail in the previous rejection made under 35 U.S.C. § 101 (see paragraph 18). Although the EL-246 antibody was shown to inhibit leukocyte binding in vitro and in vivo in an animal model, no clear nexus has appeared in the application to predict E-/L-selectin-specific immunotherapy of human diseases. Therefore it does not appear that the asserted operability of the claimed method and compositions for treating human inflammatory diseases would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone.

B) It is unclear from the specification whether any common epitope, as recited in independent claim 1, found on E-selectin and L-selectin can serve as a diagnostic or therapeutic agent as the disclosed utility of the instant application. Applicant has exemplified only the common epitope between E-/L-selectins defined by the EL-246-specific antibody. There is no evidence relating to another common epitope between E-/L-selectins to enable the diagnostic and therapeutic utilities embraced by the instant invention. The disclosure is not enabled for any common antigenic determinant found on E-selectin and L-selectin, all of which are embraced by the claims. The specification has not provided sufficient direction or guidance to one of skill in the art to properly select a E-/L-selectin common epitope other than that defined by the EL-246 antibody which may provide diagnostic or therapeutic operability. It appears that undue experimentation would be required of one skilled in the art to practice the broadly claimed specificity of common antigenic determinants found on E-/L-selectins using the teaching of the specification alone.

Applicant should limit claims to the common E-/L-specific antigenic determinant defined by the EL-246 antibody.

C) It is apparent that the EL-246 antibody is required to practice the claimed invention as disclosed in the specification and cited in the claims. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the EL-246 hybridoma. See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining the EL-246 antibody and it does not appear to be a readily available material. Deposit of the EL-246 hybridoma would satisfy the enablement requirements of 35 U.S.C. 112.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

- a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;
- b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;
- c) the deposit will be maintained for a term of at least thirty years and at least five years after the most recent request for the furnishing of a sample of the deposited material;
- d) a viability statement in accordance with the provisions of 37 CFR 1.807; and
- e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CFR 1.809 (d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

21. Claims 1-33 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification (see paragraphs 19-20).

22. Claims 10-17 and 26-29 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-17 and 26-29 are indefinite in the recitation of "selectin molecules expressed on the surface of leukocytes and endothelial cells" (claims 10-16), "short consensus region express on the surface of leukocytes" (claim 17) and "to L-selectin and E-selectin" (claims 26-29) because the characteristics of the antibody specificity is not known. Also, this language is vague and indefinite since it encompasses potentially thousands of different selectin specificities and it is not apparent from the disclosure which particular specificity is being referred to. Applicant has disclosed particular characteristics concerning the epitope and functional specificities of selectin-specific antibodies, as exemplified by the EL-246 antibody. No evidence is provided that any selectin-

specific antibody with the claimed characteristics would have utility. It appears that undue experimentation would be required of one skilled in the art to enable the claimed methods using the teaching of the specification alone.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

Again, applicant should limit claims to the common E-/L-specific antigenic determinant defined by the EL-246 antibody.

23. Claims 1-33 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1, 3, 4, 6, 8, 18-25 and 30-33 are indefinite in the recitation of "common antigenic determinant" because its characteristics are not clear. Amendment should define the E-/L-specific common determinant by the EL-246 antibody. See section 20 B above.

B) Claims 1, 3, 4, 6, 8 and 18-33 are indefinite in the recitation of "capable of recognizing" and "capable of inhibiting" because it unclear what is intended by this phrase. Amendment should replace such phrase with positive language such as "which specifically binds" or "which specifically inhibits".

C) Claim 2 is indefinite in the recitation of "EL 246" because its appropriate designation is "EL-246". Applicant should be consistent in terminology.

D) Claims 8-9 are indefinite in the recitation of "suspecting" because "suspected" is the more appropriate word.

E) Claims 10-17 are indefinite in the recitation of "with the intent of reducing of tissue damage" because the characteristics of this phrase are not known. Amendment should either delete this phrase or state the function in positive terms.

F) Claim 29 is indefinite in the recitation of "similar" because the characteristics of this term are not clear. What are the metes and bounds of similar?

G) Claims 30-31 are indefinite in the recitation "endothelial cell layer" because "endothelial cells" is the more appropriate term.

The amendments must be supported by the specification so as not to add any new matter.

23. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(f) he did not himself invent the subject matter sought to be patented.

24. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

25. Claims 1-8 and 19-25 are rejected under 35 U.S.C. § 102(f) because the applicants did not invent the claimed subject matter. The characterization of the common antigenic determinant of E-/L-selectin as exemplified by the EL-246 antibody as described in the instant application is cited in Jutila et al. (1449, #40; J.Exp. Med., 1992). This reference presents an ambiguity with regard to inventorship because the named authors includes Watts, Walcheck and Kansas who are not listed as inventors herein. This reference says nothing about inventorship. The reference is written as "we characterized". Because of this ambiguity, it is incumbent on applicant to provide a satisfactory showing which would lead to a reasonable conclusion that applicant alone is the inventor of the claimed invention. See In re Katz, 687 F.2d 450,

215 USPQ 14(CCPA 1982). To resolve the ambiguity, applicant may file declarations by the non-applicant co-authors of the reference disclaiming the invention or a declaration by applicant setting forth the facts which provide an explanation as to why the non-applicant co-authors are not inventors. See MPEP 715.05.

26. Claims 1, 6, 18, 19, 21-25 are rejected under 35 U.S.C. § 102(b) as anticipated by Kishimoto et al. (1449, #38; PNAS, 1990, see entire document) as evidenced by Jutila et al. (1449, #40; J. Exp. Med., 1992). The claimed antibody specificity is drawn to a common epitope of E-/L-selectins. Applicant has exemplified the EL-246 monoclonal antibody. Kishimoto et al. teach the DREG-56 antibody, which was described as a L-selectin-specific antibody which could inhibit leukocyte binding. Kishimoto et al. also teach the generation of L-selectin-specific monoclonal antibodies. Kishimoto et al. teach the use of such antibodies for detecting L-selectin that is regulated during inflammation and for inhibiting inflammation in vivo. A pharmaceutically acceptable carrier such as PBS was well known in the art as solvent for immunoglobulins for storage and immunoassays. Kishimoto et al. did not recognize its E-selectin specificity. Jutila et al. teach that the DREG-56 has the same or nearly the same binding specificities of the exemplified EL-246 monoclonal antibody (see entire document, particularly Figure 7 and page 1571, column 1, lines 3-6). Jutila et al. also teach some distinctions between the DREG 56 and the EL-246 antibodies (see Table 1). The rejected claims do not recite the particular limitations that distinguish between DREG 56 and EL-246 (intended invention) specificities.

The applicant is invited to amend the claims to recite the particular common E-/L-specific epitope recognized by the EL-246 antibody disclosed by the instant application to obviate this rejection.

27. Claims 1-33 are rejected under 35 U.S.C. § 103 as being unpatentable over Kishimoto et al. (1449, # 38) in view of Lasky et al. (1449, U.S. Patent No. 5,098,833), Bevilacqua et al. (1449, U.S. Patent No. 5,081,034) and Watson et al. (1449, #23; Nature, 1991). In addition, Jutila et al. (1449, #40; J. Exp. Med., 1992) is provided as pertinent art of record. Claims 1-33 are drawn to antibodies that recognize a common E-/L-selectin epitope and their use in diagnosis and therapy. Kishimoto et al. teach the derivation of a number of L-selectin-specific antibodies including the DREG-56 antibody (see entire document). Kishimoto et al. teach the ability of the DREG-56 antibody to inhibit lymphocyte-endothelial binding in vitro. Kishimoto et al. also compare these observations with the ability of other L-selectin-specific antibodies to inhibit neutrophils and monocytes

in addition to lymphocytes, which are useful for treating inflammation in vivo. Kishimoto et al. did not recognize that DREG-56 recognized a common E-/L-selectin epitope per se. Lasky et al. teach the cloning of L-selectin and its use in the diagnosis and treatment of inflammatory diseases (see entire document). Similarly, Bevilacqua et al. teach the cloning E-selectin and its use in the diagnosis and treatment of inflammatory diseases. As disclosed in the specification, the prior art is replete of examples of L-selectin and E-selectin antibodies which inhibit various models of inflammatory diseases (see pages 1-10 of the specification). Watson et al. teach the use of L-selectin-specific molecules as therapeutic agents to inhibit viral infection or immune function (see entire document). Furthermore, Watson et al. teach that combinations of adhesion molecules may be required to to inhibit acute or chronic inflammatory responses (see page 166, column 2, paragraph 3). Here, Watson et al. corresponds the inhibitory effects of the L-selectin chimeric protein and E-selectin expression. Watson teaches that the rational design of anti-inflammatory regents should be based on competitive blocking of leukocyte-endothelial cell interactions.

Applicant has characterized the property of the EL-246 antibody as being directed towards a common E-/L-selectin epitope. Such specificity was already selected for by routine screening of L-selectin-specific antibodies that inhibited leukocyte-endothelial interactions and their use as diagnostic and therapeutic agents for human inflammatory diseases, as evidenced by the DREG-56 antibody. The claimed limitations of antibodies specific for (common) E-/L-selectin epitopes or short consensus regions would have been met by the selection process disclosed in the prior art. The claimed limitations of inhibiting adhesion, leukocyte rolling, tissue damage, and inflammation would have been met by the selection for treating inflammatory diseases, as disclosed in the prior art.

Jutila et al. is cited as pertinent art of record but not relied upon as prior art. Jutila et al. teach that the DREG-56 has the same or nearly the same binding specificities of the exemplified EL-246 monoclonal antibody (see entire document, particularly Figure 7 and page 1571, column 1, lines 3-6). Although Jutila et al. also teach some distinctions between the DREG 56 and the EL-246 antibodies (see Table 1), the burden is on the applicant to establish a patentable distinction between the claimed and referenced antibodies and methods. Applicant is reminded that in submitting evidence asserted to establish differences and/or unobvious results sufficient to dissipate a prima facie case of obviousness, there is a burden on the patent applicant to establish not only that the differences in results achieved are in fact "unexpected and unobvious" but also to


establish that the differences are of practical significance. See 27 USPQ2d Ex parte C (see page 1497, column 1, paragraph 4). It is not clear that a patentable distinction can be made upon differences in binding L-selectin from different species. The critical element remains in the selection for E-/L-selectin-specific antibodies to inhibit inflammatory processes in humans.


One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of L-selectin-specific antibodies as therapeutic and diagnostic reagents in treating human inflammatory diseases. The derivation of those antibodies which bind a common E-/L-selectin would have been a result of selecting for these properties, as evidenced by the DREG-56 antibody. Furthermore, the ordinary artisan would have coordinated addressing multiple adhesion molecules in the rational design of anti-inflammatory reagents including the relationship of E-selectin and L-selectin in leukocyte-endothelial interactions. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

28. No claim is allowed.

29. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.


Phillip Gambel, Ph.D.
May 27, 1994


DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180

5/31/94